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Deep repetitive TMS with the H7 coil is sufficient to treat comorbid MDD and OCD

Obsessive-compulsive disorder (OCD) is a neuropsychiatric illness affecting 2–3% of the United States population during their lifetime [1]. Patients frequently have additional psychiatric illness at the time of diagnosis or at other times in their lifetime. The most common comorbid diagnosis is major depressive disorder (MDD) [2]. In 2018, the US Food and Drug Administration cleared the treatment of resistant OCD with high frequency deep repetitive transcranial magnetic stimulation (dTMS) over the dorsomedial prefrontal and anterior cingulate cortices (DMPFC-ACC) with the H7 coil, based on the efficacious results of a multicenter study [3]. The H7 coil and stimulated target are significantly different from the H1 coil which is cleared for the treatment of resistant MDD and stimulates the left prefrontal cortex more than the medial and right prefrontal cortices. It was not clear whether patients with comorbid MDD and OCD would require two different TMS treatments, with the H1 and H7 respectively, or would the OCD

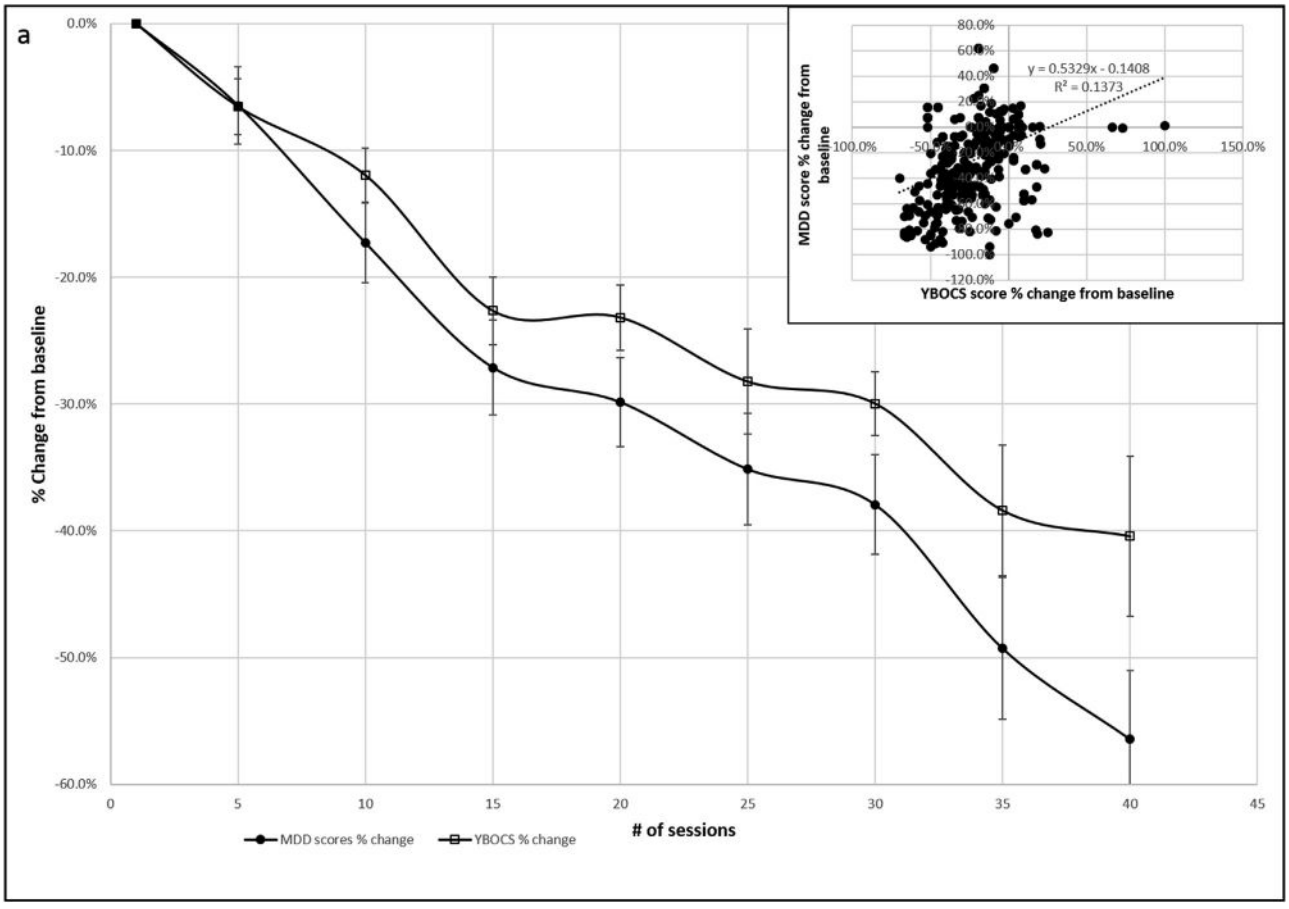

Fig. 1. a. Improvement in clinical symptoms of comorbid OCD-MDD patients. Mean ± SEM percent change in YBOCS and MDD scores from baseline as a function of number of dTMS sessions. Scatter plot is shown in the top right panel. b. Individual % change in YBOCS score after 30 sessions (partial response: ≥ 20%; full response: ≥ 30%). c. Individual % change in MDD score after 30 sessions (partial response: ≥ 25%; full response: ≥ 50%).

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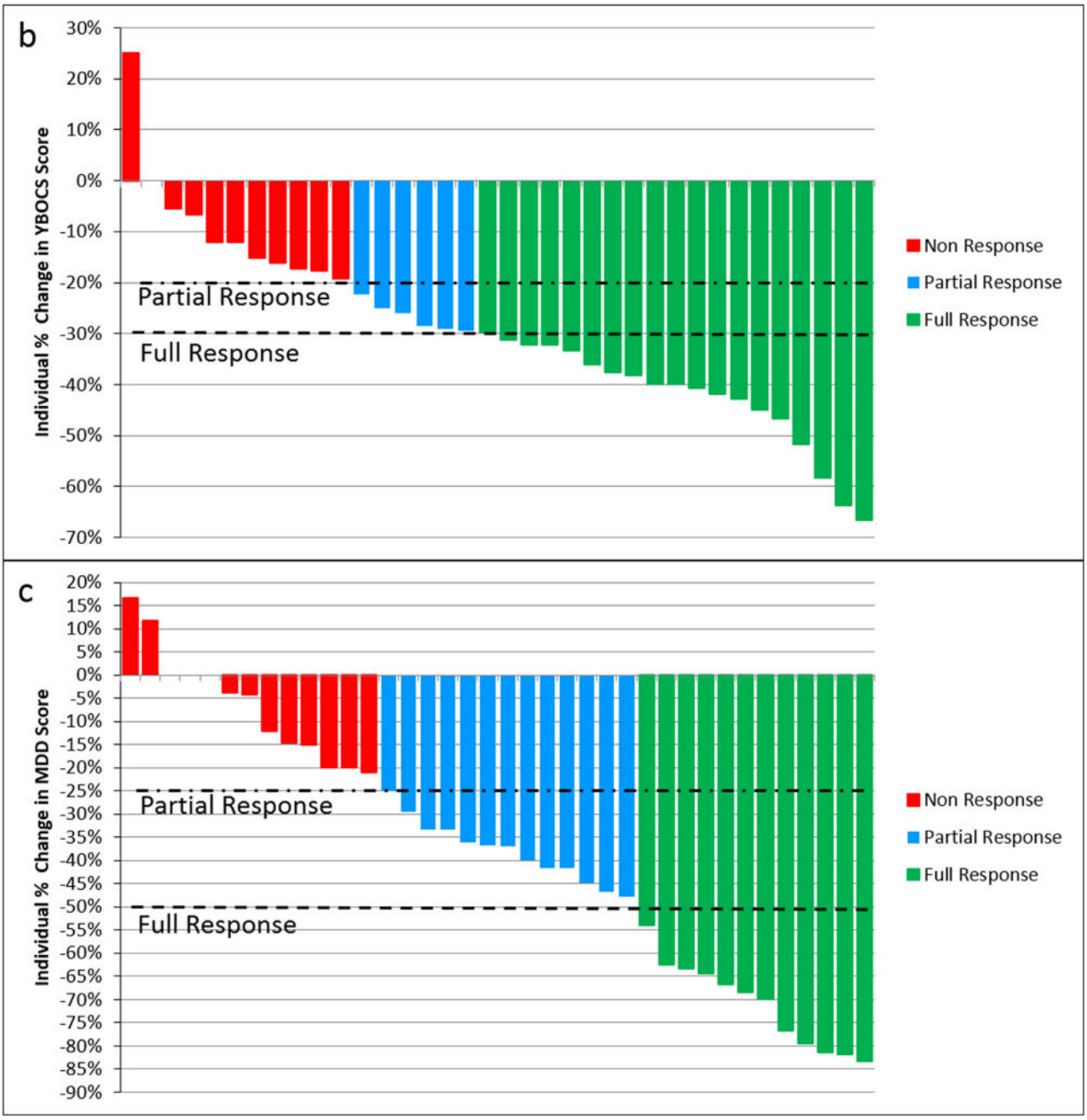

Fig. 1. (*continued*).

treatment with the H7 also treat their MDD. A post hoc analysis of the multicenter study identified a subset of patients with comorbid OCD-MDD (HDRS21 $\geq$ 16) and found a statistically significant decrease in HDRS scores from baseline at all time points ($p < 0.05$ for weeks 2–4, $p < 0.01$ for week 6, $p < 0.005$ for 1-month follow-up) in the active dTMS group ($N = 9$) but not in the sham ($N = 10$) [4]. The decrease in HDRS from baseline was not statistically significant from sham, due to the small sample size. To continue to assess this question, we sought to analyze a larger sample of subjects with comorbid OCD-MDD for their MDD outcomes when they were only treated with the H7 coil.

The population has been previously described, and the study has an institutional review board exemption from informed consent [5]. Tailored provocation preceded each dTMS session as previously described [3,5,6]. Patients were treated with the FDA-cleared dTMS protocol of 20 Hz at 100% resting foot motor threshold, with 2 sec pulse trains and 20 sec intertrain intervals, for a total of 50 trains and 2000 pulses per session [3]. All sites with H coils are solicited to participate in post marketing data collection. This population was required to have had a diagnosis of OCD, outcome measures with the Yale Brown Obsessive Compulsive Scale (YBOCS), a comorbid diagnosis of at least moderate MDD with any of several rating

scales, and treatment with the H7 coil and not any additional coils. Depression severity inclusion criteria was defined as a Hamilton depression rating scale (HDRS) HDRS-21 Total Score ≥16, the Patient Health Questionnaire-9 (PHQ-9) PHQ-9 Total Score ≥10, the Beck Depression Inventory-II (BDI-II) BDI-II Total Score ≥20 and the Inventory of Depressive Symptomatology- Self Report (IDS-SR) IDS-SR Total Score ≥24. At every time point, the average percent change in all the available MDD scores was determined and used for analysis.

A total of 59 OCD patients (YBOCS ≥20) with at least moderate MDD at baseline were treated with H7 dTMS. A significant decrease was seen in both YBOCS and MDD scores after 5 dTMS sessions and at any timepoint beyond (Fig. 1a). After 30 sessions, YBOCS score decreased on average by 30% and MDD scores by 38%, with the vast majority (71.4%) of patients demonstrating benefit from treatment in both disorders (Fig. 1b&c). A continuous improvement was seen upon further dTMS sessions up to 40 sessions. A highly significant correlation was found between YBOCS and MDD scores change ($p < 0.0001$, Spearman $\mathbf{r} = 0.3923$, 384 pairs; Fig. 1a, top right panel). Insert Fig. 1.

The currently reported results corroborate our previous finding in a larger sample and further elucidate the underlying mechanism of the demonstrated improvement in MDD following OCD dTMS treatment with the H7 coil.

While it could be argued that the improvement in MDD is simply an indirect result of alleviating the OCD symptoms, a more compelling hypothesis is that the stimulation over the DMPFC-ACC directly improves MDD symptoms irrespective of the OCD. The dmPFC functions as a hyper-connected hub between distinct distributed neural networks involved in depression and together with the adjacent ACC forms the most consistent region to show gray matter reduction in MDD patients [7]. In recent years evidence has accumulated demonstrating that HF stimulation of the dmPFC and ACC with deeper coils is sufficient for MDD [8,9], though a recent blinded trial over dmPFC with a figure- 8 coil did not demonstrate superiority over sham [10], likely due to the lower depth and volume of the stimulation. MDD is a heterogenous syndrome that encompasses varied co-occurring symptoms and divergent responses to treatment. To date, evidence for associations between clinical symptoms and the putative underlying brain circuits in MDD are inconsistent and variable at the individual level. Recently, biological subtyping (clustering of individuals with potential biomarkers) has been recognized as a promising approach for elucidation of the heterogeneity of depression. Unlike the conventional diagnostic categories, the biological subtypes (i.e., biotypes) of depression bridge diagnoses and biomarkers and overlap, interact, or co-occur in patients with MDD at the individual level. Unfortunately, existing findings are inconsistent, and reveal profiles of neural hypoactivity and hyperactivity, both hypoconnectivity and hyperconnectivity, within the broad diagnostic categories of depression and anxiety. These variations might show the contribution of multiple biotypes of underlying neural circuit dysfunction that cut across existing diagnostic categories. Drysdale et al. [11] have identified anhedonia/psychomotor retardation and anxiety/insomnia as distinct biotypes in MDD, corresponding to distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks. Consistent with this is a more recent finding of distinct dysphoric and anxiosomatic circuit targets [12]. In the former, the anxiety/insomnia biotype was preferentially responsive to dorsomedial prefrontal rTMS, which aligns with the latter's anxiosomatic target. It would stand to reason that comorbid OCD-MDD patients' circuit disfunction maps onto these targets, explaining the demonstrated benefit from a DMPFC-ACC dTMS treatment with the H7 coil.

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Declaration of competing interest

Dr. Tendler serves as Chief Medical Officer of and has a financial interest in BrainsWay, as well as a commercial/research TMS center. Dr. Roth is a key inventor of the Deep TMS technology and has a financial interest in BrainsWay. Dr. Harmelech is a BrainsWay employee.

References

[1] Association AP. Diagnostic and statistical manual of mental disorders. fifth ed. American Psychiatric Publishing; 2013 (DSM-5(TM)). 5th ed.
[2] Pallanti S, Grassi G, Sarrecchia ED, Cantisani A, Pellegrini M. Obsessive-compulsive disorder comorbidity: clinical assessment and therapeutic implications. Front Psychiatr 2011;2:70. https://doi.org/10.3389/fpsyt.2011.00070.
[3] Carmi L, Tendler A, Bystritsky A, Hollander E, Blumberger DM, Daskalakis J, et al. Efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder: a prospective multicenter randomized double-blind placebo-controlled trial. Am J Psychiatr 2019. https://doi.org/10.1176/appi.ajp.2019.18101180. appiajp.201918101180.
[4] Harmelech T, Tendler A, Roth Y, Zangen A. Do comorbid OCD-MDD patients need two separate dTMS protocols? Brain Stimulat 2020;13:1000–1. https://doi.org/10.1016/j.brs.2020.03.014.
[5] Roth Y, Tendler A, Arikan MK, Vidrine R, Kent D, Muir O, et al. Real-world efficacy of deep TMS for obsessive-compulsive disorder: post-marketing data collected from twenty-two clinical sites. J Psychiatr Res 2020. https://doi.org/10.1016/j.jpsychires.2020.11.009.
[6] Tendler A, Sisko E, Barnea-ygael N, Zangen A, Storch EA. A method to provoke obsessive compulsive symptoms for basic research and clinical interventions. Front Psychiatr 2019;10:814.
[7] Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc Natl Acad Sci USA 2010;107:11020–5. https://doi.org/10.1073/pnas.1000446107.
[8] Tendler A, Sisko E, Barnea-Ygael N, DeLuca M, Rodriguez N, Corbett-Methott S, et al. Antidepressant remission to dTMS of the dmPFC and ACC in lateral PFC dTMS nonresponders: case series. Brain Stimulat 2017;10:714–5. https://doi.org/10.1016/j.brs.2017.01.579.
[9] Kreuzer PM, Schecklmann M, Lehner A, Wetter TC, Poeppl TB, Rupprecht R, et al. The ACDC pilot trial: targeting the anterior cingulate by double cone coil rTMS for the treatment of depression. Brain Stimulat 2015;8:240–6. https://doi.org/10.1016/j.brs.2014.11.014.
[10] Dunlop K, Sheen J, Schulze L, Fettes P, Mansouri F, Feffer K, et al. Dorsomedial prefrontal cortex repetitive transcranial magnetic stimulation for treatment-refractory major depressive disorder: a three-arm, blinded, randomized controlled trial. Brain Stimulat 2019. https://doi.org/10.1016/j.brs.2019.10.020.
[11] Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med 2017;23:28–38. https://doi.org/10.1038/nm.4246.
[12] Siddiqi SH, Taylor SF, Cooke D, Pascual-Leone A, George MS, Fox MD. Distinct symptom-specific treatment targets for circuit-based neuromodulation. Am J Psychiatr 2020;177:435–46. https://doi.org/10.1176/appi.ajp.2019.19090915.

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